B3 carboxyl acid group have been ionically crosslinked by said trivalent cations and the adhesion preventative has a viscosity of at least 2,500 cps. --

REMARKS

The rejection of claims 1-6, 8 and 13-16 under 35 U.S.C. §102(b) as being anticipated by GALATIK et al. (Czechoslovakian Patent No. 264,719) has been considered. However, Applicants respectfully request reconsideration of this rejection.

GALATIK et al. describes complexes of hyaluronate of an alkali metal with a multivalent cation selected from the group consisting of Mg^{2+}, Ca^{2+}, Zn^{2+}, Ba^{2+}, Al^{3+}, Cu^{2+}, Zr^{4+}, Cr^{3+}, Fe^{3+}, where the molar composition of the complex is 0.1 to 5 moles of hyaluronate to 1 to 25 moles of coordinate cations. This is equivalent to a range of 0.2 moles to 250 moles of cation per mole of hyaluronate.

In the Declaration under 37 C.F.R. §1.132 of Dr. Douglas B. Johns filed herewith, the examples presented in GALATIK were examined to determine whether a monomer or polymer formed the basis of the calculations. Examples 2, 3, and 4 of GALATIK assume the reader knows the answer to the "mole question", and disclose a dimer, 1.5mer and dimer, respectively, which are not contemplated by the present invention as claimed. Examples 1, 5, and 6 provide sufficient information to make calculations using the different molecular weights for hyaluronate, i.e. monomer (401 g/mole) or polymer (either 300,000 or 8,000,000 g/mole). Examination of these calculations leads one to the

conclusion that the polymer molecular weight had to be used in the calculations for the examples to be within the claim of 0.2 to 250 moles of cation per mole of hyaluronate.

As calculated in the attached 1.132 Declaration of Dr. Douglas B. Johns, the maximum amount of cations used by Galatik et al. would be sufficient to theoretically crosslink less than 60 percent of the carboxyl groups of a hyaluronate polymer with an average molecular weight of 550,000 or greater. Further, Galatik specifically mentions commercially available sodium hyaluronate, HEALON being exemplary, at the third full paragraph of page 2. Since no other information is provided, it is appropriately presumed that these are the materials used under GALATIK, and that they are obtained commercially as such. It is generally known that HEALON has a molecular weight of 1,000,000 - 2,000,000. Therefore, the crosslinking density will be significantly less than 55 percent.

Claim 1 as amended requires the hyaluronate to be crosslinked with an amount of cations sufficient to theoretically crosslink greater than 60 percent of the carboxyl groups of the hyaluronate. This is equivalent to a molar ratio of cation to hyaluronate of from about 413 to about 6016 for a hyaluronate molecular weight range of 550,000 to 8,000,000. Therefore, claim 1 as amended and dependent claims 2-4, 6, 8, and 13-16 are not anticipated by Galatik et al.

Additionally, Applicants respectfully submit that Galatik is nonenabling for hyaluronate with a molecular weight below 500,000. As is described by Balazs and EPO 138 572 A2, a copy of which is filed herewith, hyaluronate, unless appropriately purified contains contaminants, which cause cell migration and inflammation. Balazs describes the

use of ultra-pure hyaluronate as being useful to prevent excess fibrous tissue formation and the consequential development of adhesions and scars. See column 14, line 11 et seq. of Balazs. EPO 138,572 A2 describes a second hyaluronate fraction that can also be used that does not cause cell migration and inflammation. EPO 138,572 A2 describes a hyaluronate fraction with an average molecular weight from 500,000 to about 730,000, which does not cause cell migration or inflammation. However, though EPO 138,572 A2 does disclose hyaluronate fractions with a molecular weight below 500,000, these fractions cause cell migration. Thus, Applicants respectfully submit that contrary to Galatik's teaching, hyaluronate with an average molecular weight below 500,000 is unsuitable for use in the prevention of adhesions. Therefore, Applicants submit that Galatik is not enabling for hyaluronate with an average molecular weight below 500,000.

The rejection of claims 7 and 17 under 35 U.S.C. §103 as being unpatentable over Galatik et al. further in view of Balazs (U.S. 4,141,983) and Shimizu et al. (U.S. 4,024,073) has been reviewed. Applicants, however, respectfully submit that this rejection is in error and requests reconsideration of this rejection.

Claims 7 and 17 are dependent on claim 1, which has been amended to incorporate language from claim 5. As discussed above, the amendment to claim 1 and, therefore, claims 7 and 17 distinguish the claimed invention from Galatik et al. Galatik et al. describes forming dimers, trimers higher order complexes of hyaluronate and a multivalent cation. Galatik et al. also suggests on page 2 in paragraph 5 that the effectiveness of hyaluronate is directly proportional to its specific molecular weight. Galatik et al. on page 3

in paragraph 1-2 suggests that his crosslinked hyaluronate complexes also will have increased efficacy with increasing "effective" molecular weight (as measured by viscosity). Unfortunately, Galatik et al. neither recognizes nor appreciates that the "effective" molecular weight of the hyaluronate is not the most important factor in preventing adhesions.

Applicants have unexpectedly discovered that the "effective" molecular weight of crosslinked hyaluronate is not indicative of hyaluronate's effectiveness in preventing adhesions. Applicants have discovered that by using hyaluronate composition with crosslinking densities outside of the ranges described by Galatik that significantly more effective adhesion prevention can be obtained. In Example 5, Applicants present numerous experiments with the rabbit uterine horn and rabbit sidewall adhesion models having various viscosities and crosslinking densities. In Table 4, the effective viscosity of the crosslinked and uncrosslinked hyaluronate do not correlate well with the percentages of adhesion which is contrary to the teaching of Galatik. However, Table 4 does demonstrate that there is a strong correlation between the crosslinking density and adhesion prevention. Table 5 also demonstrates a direct correlation between crosslinking density and reduction of adhesions. Table 6 presents data from several rabbit uterine horn adhesions studies. In the rabbit uterine horn model it is significantly more difficult to avoid adhesions. The first three entries in Table 6 are uncrosslinked samples of hyaluronate of varying concentrations and viscosities, the remainder of the entries are crosslinked hyaluronate samples. Table 6 shows a correlation between crosslinking density and adhesion reduction. The claims of the present application distinguish over Galatik by requiring a crosslinking density (percent crosslinking)

outside the ranges described by Galatik which provides an unexpected improvement in adhesion prevention. Therefore, Applicants respectfully submit that claims 7 and 17 are patentable over Galatik.

Balazs describes ultra-pure, high molecular weight hyaluronic acid having an average molecular weight greater than 750,000, preferably greater than 1,200,000 and a limiting viscosity of greater than about 1400 gram cm^3/g and preferably greater than 2000 cm^3/g. Balazs also describes the use of ultra-pure high molecular weight hyaluronic acid to prevent post-operative adhesions which may occur between healing tissues. Balazs, however, neither discloses nor suggests the use of hyaluronate crosslinked with a multivalent cation provided in an amount sufficient to crosslink in the range of from about 60 to about 100 percent of the carboxyl groups of the hyaluronate for preventing adhesions. Further, as shown by Tables 4, 5, and 6 of Example 5, crosslinking densities in this range result in improved adhesion prevention. Therefore, Applicants respectfully submit that the present claims are patentable over Balazs alone or in combination with Galatik.

Shimizu et al. describes a hydrogel containing a chelating agent bound to a water-soluble polymer and a polyvalent metal ion crosslinking the polymer molecules through the chelating agent. Shimizu describes novel stable, elastic hydrogel for use as a sustained-released medicament carrier, as an electrophoresis, as a carrier for insoluble enzymes and as an adduct for foods.

Shimizu describes hydrogel as composed of **three** components: a water soluble polymer; a chelating residue; and a metal ion. The chelating molecules are attached to the

backbone of water soluble polymers and then crosslinked with a metal ion to form the hydrogel. Suitable chelating molecules in addition to the chelating forming functional groups, must have another functional group through which chelating entities are bound to the polymer chain. Shimizu proposes combining certain drugs or medicaments which will be entrapped in the hydrogel such as drugs having a molecular weight of more than 3000. These drugs useful in this hydrogel include insulin, interferon, double standard complex of polyinosinic and polycytidylic acid, urease, catalase, uricase, glucose isomerase and asparaginase.

Shimizu does not disclose or suggest eliminating the chelating molecules from his hydrogel. Shimizu also does not disclose or suggest using his hydrogel for adhesion prevention. Thus, Shimizu does not disclose or suggest the claimed invention which is the use of hyaluronate that has an ionically crosslinked crosslinking density of greater than 60 percent to prevent or reduce the incidence of post-operative adhesions. Accordingly, the present invention as claimed is patentably distinguishable over Shimizu.

Applicants respectfully submit that there is no suggestion or disclosure in Galatik, Balazs or Shimizu for using hyaluronate with an ionic crosslinking density above 60 percent to prevent or reduce post-operative adhesions. The only suggestion to use the claimed highly crosslinked hyaluronate in the prevention of adhesions is provided by the Applicants. The PTO has the burden under section 103 of establishing a *prima facie* case of obviousness. This burden can only be satisfied by showing some objective teaching in the prior art or that knowledge generally available in the art would lead one of ordinary skill in

the art to combine the relevant teachings of the reference. See In re Fine, 5 U.S.P.Q. 2d 1596, 1598 (Fed. Cir. 1988). There is no suggestion or teaching in the art applied, Galatik, Balazs, or Shimizu to motivate one skilled in the art to use hyaluronate with an ionic crosslinking density above 60 percent to prevent or reduce post-operative adhesions. Additionally, neither Galatik, Balazs, nor Shimizu recognized or appreciated that using hyaluronate with an ionic crosslinking density above 60 percent would significantly reduce the incidence of post-operative adhesion formation. Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 7 and 17.

The rejection of claims 9-12 under 35 U.S.C. §103 as being unpatentable over Galatik et al. as applied to claims 1-6 and 8 above and further in view of Applicants' disclosure at page 10, lines 15-27 has been considered.

Applicants respectfully submit that claim 1-6 and 8 are patentable over Galatik for the reasons discussed above, therefore, claims 9-12 are also patentable.

In view of the foregoing, the application is now believed to be in condition for allowance. Early and favorable action thereon is requested.

Respectfully submitted,

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Dated: June 23, 1995

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